DESENSITIZATION PROTOCOLS FOR ANTIBIOTICS AND OTHER MEDICATIONS

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Introduction

Acute drug desensitization is the process by which a drug-allergic individual is converted from a highly sensitive state to a state in which the drug is tolerated. The procedure involves the cautious administration of incremental doses of the drug over a period of hours to days and it is used primarily in the management of IgE-mediated drug hypersensitivity reactions. More recently, this technique also has been used successfully in the management of other forms of immunopathology.

Acute desensitization may be considered in those patients in whom IgE antibodies to a particular drug are known or are presumed to exist and no alternative treatment agent is available. In addition, drug desensitization may be effective for other reactions that are delayed in onset, that appear to be immune in nature, but that are not IgE-mediated. While most of the desensitization protocols have involved beta-lactam antibiotics (1-4), this principal has been applied successfully to other agents as well (5-7) that include: other antibiotics, insulin, chemotherapeutic agents, vaccines, heterologous sera and other proteins (Tables I and II).

TABLE I. SUCCESSFUL ANTIBIOTIC DESENSITIZATIONS

Penicillins	Cephalosporins
Sulfonamides	Vancomycin
Aminoglycosides	Pentamidine
Clindamycin	Anti-tubercular agents

TABLE II. SUCCESSFUL DESENSITIZATIONS TO OTHER AGENTS

Chemotherapeutics	Corticotropin
Insulin	Heparin
LHRH	Antivenoms
Measles vaccine	Heterologous sera
Tetanus toxoid	Deferoxamine
D-penicillamine	Carbamazepine

Mechanism(s) Responsible for Acute Desensitization

In studies of patients who were shown to have penicillin-specific IgE antibodies and who underwent successful penicillin desensitization, the data suggest that antigen-specific, mast cell desensitization is responsible for the tolerant state (1,4,8). Mediator depletion appears to play no role (5). The fact that wheal-and-flare skin test responses to penicillin oftentimes become negative with successful desensitization, while other IgE antigen responses remain unchanged, also supports the involvement of an antigen-specific mechanism (2,4,5). Interestingly, both clinical reactivity and skin test reactivity return within a few days unless a chronic tolerant state is maintained by continued drug administration. This finding indicates that the desensitized state is dependent upon the continuous presence of antigen and that clinical sensitivity returns rapidly in the absence of antigen.

The underlying mechanism responsible for the antigen-specific desensitized state remains unclear. Sullivan (5) hypothesizes that IgE receptor aggregation may generate counter-regulatory forces that, instead of causing cell activation, actually extinguishes activating signals. During desensitization, the drug is introduced slowly, and drug concentrations rise gradually. Thus, it is possible that slow rates of receptor aggregation caused by the gradual increase in drug concentration, along with suppression of cellular activation signals, may lead to antigen-specific desensitization and clinical tolerance. In addition, it is likely that during the

desensitization process, univalent drug-haptenated proteins are formed and contribute to the desensitized state by inhibiting the cross-linking of drug-specific IgE molecules on mast cells. The finding that monovalent haptens can specifically inhibit allergic drug reactions (9,10) further supports a role for hapten inhibition in drug desensitization.

Desensitization Procedure

Drug desensitization should be performed with the drug that is required for therapy and either the oral or intravenous route may be used. The starting dose for the procedure can be determined by performing intradermal skin tests with the native drug at a dose that does not cause a nonspecific irritant reaction. For example, if a 0.02 ml intradermal injection of a drug at a 1 mg/ml concentration does not cause a local or systemic reaction, oral desensitization may be started at the dose injected (i.e., the tolerated dose, 20 µg). Parenteral desensitization typically begins with 1/10 or 1/100 of the dose that was administered intradermally.

Rapid desensitization protocols occur over several hours. Drug doses typically are doubled every 15 minutes and vital signs and peak flow values are monitored before and throughout the procedure. Mild complications of drug desensitization include pruritus or pruritic rashes and these complications may occur in up to one third of the desensitizations performed. These reactions may require adjustments in dosing/and or intervals as well as the use of symptomatic medications. If more severe complications occur, such as bronchospasm or hypotension, the next dose should be reduced greater than ten-fold and repeated until no systemic reactions are observed. In some instances, the desensitization procedure may have to be aborted.

It is critical that the individuals involved with the desensitization procedure (nurses, physicians, etc.) understand that this is a serious procedure. While anaphylactic reactions rarely occur if conservative protocols are used, health care personnel must be prepared to treat anaphylaxis if it does happen. It is also critical that both the patient and the healthcare personnel understand the importance of uninterrupted therapy after the procedure is completed since anaphylactic sensitivity, most likely, will return after the drug is withdrawn.

Rapid “generic” antibiotic desensitization protocol (oral)

Step	Concentration mg/ml	Amount ml	Dose mg	Cumulative dose (mg)
1	0.05	0.1	0.005	0.005
2	0.05	0.2	0.01	0.015
3	0.05	0.4	0.02	0.035
4	0.05	1.0	0.05	0.085
5	0.5	0.2	0.10	0.185
6	0.5	0.4	0.2	0.385
7	0.5	0.8	0.4	0.785
8	0.5	1.6	0.80	1.585
9	0.5	3.0	1.5	3
10	0.5	6.0	3.0	6
11	0.5	10.0	5.0	11
12	0.5	20.0	10.0	21
13	0.5	40.0	20.0	41
14	50	1	50.0	91
15	50	2	100.0	191

16	50	4	200.0	391
17	50	10	500.0	891

From Sullivan TJ. Drug Allergy. In Middleton E Jr, et al, Eds. Allergy:Principles and Practice, 4th Edition, St. Louis: Mosby 1993.

Rapid oral SMX-TMP desensitization

Dose number	Drug Concentration	Amount	Dose	Cumulative Dose
1	0.4 mg/ml (1:100)	0.1 cc	0.04 mg	0.04 mg
2	same	0.2 cc	0.08 mg	0.12
3	same	0.4 cc	0.16 mg	0.28
4	same	0.8 cc	0.32 mg	0.6
5	same	1.6 cc	0.64 mg	1.24
6	4 mg/ml (1:10)	0.2 cc	0.8 mg	2.04
7	same	0.4 cc	1.6 mg	3.64
8	same	0.8 cc	3.2 mg	6.84
9	same	1.6 cc	6.4 mg	13.24
10	40 mg/ml (neat)	0.2 cc	8 mg	21.24
11	same	0.4 cc	16 mg	37.24
12	same	0.8 cc	32 mg	69.24
13	same	1.6 cc	64 mg	133.24
14	same	3.2 cc	128 mg	261.24
15	same	6.4 cc	256 mg	517.24 mg

Bactrim suspension - 40 mg trimethoprim (TMP)/200 mg sulfamethoxazole (SMX)

For desensitization, will need two dilutions of drug (1:100 or .4 mg/ml SMX and 1:10 or 4 mg/ml). Need approximately 5 cc of each of these dilutions and aprox. 10 cc of neat drug (40 mg/ml).

Ensure desensitization is performed in a hospital setting and that personnel are skilled in treating allergic reactions. Obtain informed consent. Administer drug doses at 15 minute intervals. Monitor vital signs, perform lung exam, check peak flows every 15-30 minutes and keep a flow chart of the data. Epinephrine and H1 and H2 blockers should be by the bedside.

SMX "desensitization" protocols in patients with AIDS

Several SMX re-treatment protocols have been used successfully in patients with AIDS who develop SMX-induced rashes (non-bullous). Reintroduction of a sulfonamide by one of these protocols should not take place any earlier than one month following the initial adverse reaction nor should any of these be used in individuals with a history of Stevens-Johnson syndrome.

Sulfonamide "desensitization" protocols for patients with AIDS

Study	Desensitization	Indication	Comments

	Procedure		
Absar et al. 1994	10 days	PCP prophylaxis Isosporiasis	23/27 successfully desensitized
Moreno et al. 1995	TMP-SMX: 8 hours Sulfadiazine: 2.5 hours	CNS toxoplasmosis Nocardiosis, Isosporiasis	1/2 TMP-SMX and 7/11 sulfadiazine desensitizations were successful
Palusci et al. 1996	4 hours	PCP or PCP prophylaxis	5 children/infants who had experienced an IgE-mediated reaction to TMP-SMX were evaluated; 3/5 successfully desensitized
Caumes et al. 1997	3 days	PCP prophylaxis	37/48 successfully desensitized; factors predictive of failure were: higher CD4+ cell percentage; and higher CD4/CD8 ratio
Rich et al.	8 days	PCP prophylaxis	18/22 successfully desensitized
Demoly et al. 1998	6 hours	PCP prophylaxis	44/44 successfully desensitized on day of procedure; overall success rate at 1 month: 91% (40/44)
Yoshizawa et al. 2000	5 days	PCP prophylaxis	15/17 patients successfully desensitized

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